

Multicenter, Phase III, Randomized, Double-Blind, Placebo-Controlled Trial of Pravastatin Added to First-Line Standard Chemotherapy in Small-Cell Lung Cancer (LUNGSTAR)

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Multicenter, Phase III, Randomized, Double-Blind, Placebo-Controlled Trial of Pravastatin Added to First-Line Standard Chemotherapy in Small-Cell Lung Cancer (LUNGSTAR)

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ABSTRACT

Purpose

Treating small-cell lung cancer (SCLC) remains a therapeutic challenge. Experimental studies show that statins exert additive effects with agents, such as cisplatin, to impair tumor growth, and observational studies suggest that statins combined with anticancer therapies delay relapse and prolong life in several cancer types. To our knowledge, we report the first large, randomized, placebo-controlled, double-blind trial of a statin with standard-of-care for patients with cancer, specifically SCLC.

Patients and Methods

Patients with confirmed SCLC (limited or extensive disease) and performance status 0 to 3 were randomly assigned to receive daily pravastatin 40 mg or placebo, combined with up to six cycles of etoposide plus cisplatin or carboplatin every 3 weeks, until disease progression or intolerable toxicity. Primary end point was overall survival (OS), and secondary end points were progression-free survival (PFS), response rate, and toxicity.

Results

Eight hundred forty-six patients from 91 United Kingdom hospitals were recruited. The median age of recruited patients was 64 years of age, 43% had limited disease, and 57% had extensive disease. There were 758 deaths and 787 PFS events. No benefit was found for pravastatin, either in all patients or in several subgroups. For pravastatin versus placebo, the 2-year OS rate was 13.2% (95% CI, 10.0 to 16.7) versus 14.1% (95% CI, 10.9 to 17.7), respectively, with a hazard ratio of 1.01 (95% CI, 0.88 to 1.16; $P = .90$). The median OS was 10.6 months v 10.7 months, respectively. The median PFS was 7.7 months v 7.3 months, respectively. The median OS (pravastatin v placebo) was 14.6 months in both groups for limited disease and 9.1 months versus 8.8 months, respectively, for extensive disease. Adverse events were similar between groups.

Conclusion

Pravastatin 40 mg combined with standard SCLC therapy, although safe, does not benefit patients. Our conclusions are the same as those found in all four much smaller, randomized, placebo-controlled trials specifically designed to evaluate statin therapy in patients with cancer.

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INTRODUCTION

Small-cell lung cancer (SCLC) accounts for 15% to 20% of all new cases of lung cancer worldwide, with a low median survival of 12 to 14 months for patients with limited stage disease and 8 to 12 months for those with extensive stage disease. Although few therapeutic advances have been made over the past 40 years, there has been much

progress in the understanding of the biologic processes, including the importance of, for example, TP53 and RB1 gene mutations, and the potential for targeted therapies—for example, poly (ADP-ribose) polymerase inhibitors and immunotherapeutics—of which several trials are ongoing.¹

Statins are an inexpensive and established therapy for cardiovascular disease prevention and treatment. Despite initial concerns that long-term

ASSOCIATED CONTENT



Appendix
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use might increase the risk of developing cancer, large-scale meta-analyses of randomized trials have shown no excess cancer incidence or mortality²; however, evidence from experimental and preclinical studies has indicated that statins can inhibit tumor growth and induce apoptosis in several tumor types, including pancreatic carcinoma,³ mesothelioma,⁴ breast cancer,⁵ and SCLC cells.⁶ Mechanistically, mitogen-activated protein kinase and extracellular signal-regulated kinase upregulates antiapoptotic molecules in SCLC cells,^{7,8} and simvastatin can disrupt this process through impaired Ras superfamily signaling. This is achieved because statins block 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, thereby reducing cholesterol biosynthesis and impairing geranylation and farnesylation of Ras superfamily members.⁶ Statins could therefore act in an additive or synergistic fashion when combined with chemotherapy agents, such as paclitaxel,⁹ cisplatin,^{5,10} and doxorubicin.⁵ Experiments in H-69 human SCLC xenografts in nude mice showed impressive single-agent activity of orally administered statin.⁶ Our early studies implied that statins, such as simvastatin, would enhance the effects of single-agent or combination chemotherapy, including cisplatin and etoposide, triggering apoptosis and/or reverse chemoresistance.⁶ These effects were not confined to one platinum type because atorvastatin has subsequently been shown to enhance efficacy of carboplatin in non-SCLC cells in vitro and in vivo.¹¹ Furthermore, before our trial, an unblinded randomized trial of pravastatin in patients with liver cancer reported a striking 9-month increase in overall survival (OS).¹²

It is worth considering the large body of evidence for statins in cancer prevention or treatment, which received significant interest during major conferences held in 2015 and 2016 (ASCO, ASCO-GI, and the San Antonio Breast Cancer Symposium). Using large prospective cohort or registry studies, all but one study was positive. The magnitude of the effects found by these studies, along with study size, show why they attracted attention: a 22% reduction in cancer deaths among 146,326 women,¹³ no effect on breast cancer incidence among 79,518 women,¹⁴ 40% reduction in prostate deaths among 22,110 high-risk patients with prostate cancer,¹⁵ 14% reduction in all-cause mortality in 2,142 patients with pancreatic cancer,¹⁶ 18% reduction in recurrence and/or deaths in 8,010 patients with breast cancer,¹⁷ and 29% reduction in breast cancer mortality from a meta-analysis of 12 studies covering 87,951 patients with breast cancer.¹⁸ There have also been other large studies that have reported that statins, usually when still taken after diagnosis, can reduce recurrence or mortality in patients with esophageal,¹⁹ colorectal,²⁰ and lung cancer,²¹ and all tumors combined,²² with further evidence from meta-analyses of all cancers,²³ and prostate (postradiotherapy)^{24,25} and colorectal cancer.²⁶ However, all studies were observational and none established a dose-response for statin efficacy.

We investigated statins for the treatment of SCLC because patients are treated with platinum and/or etoposide chemotherapy, used in the earlier experimental work, and the poor prognosis made it a good candidate for an inexpensive therapy even with a modest effect.

PATIENTS AND METHODS

Etoposide and Cisplatin or Carboplatin as First-Line Chemotherapy With or without Pravastatin in Treating Patients with Small-Cell Lung Cancer

(LUNGSTAR) was a pragmatic, randomized (1:1), phase III, double-blind, placebo-controlled trial to investigate whether adding pravastatin to standard chemotherapy improves OS in patients with SCLC. Investigators are listed in Appendix Table A1 (online only). The trial had national ethics approval and was conducted according to the Declaration of Helsinki. All patients gave written informed consent.

Patients

Patients age ≥ 18 years were recruited from 91 United Kingdom National Cancer Research Network hospitals. Eligibility criteria included histologically or cytologically confirmed SCLC (limited or extensive disease), Eastern Cooperative Oncology Group performance status 0 to 3, life expectancy > 8 weeks, and adequate renal and bone marrow function. Patients were ineligible if they had mixed cell histology, prior chemoradiotherapy for the tumor, history of a malignant tumor, had used statins within the previous 12 months, or had been treated with fibrates within 4 weeks before random assignment. Patients were randomly assigned by research nurses after telephoning the University College London Cancer Trials Centre, using minimization stratified by disease status (limited ν extensive) and Eastern Cooperative Oncology Group performance status (0 to 1 ν 2 to 3).

Pravastatin or matching placebo (40 mg) were administered orally once per day from the start of chemotherapy for 2 years, unless disease progression or intolerable toxicity occurred. We used pravastatin because this seemed to be active in liver cancer¹² and, unlike other statins, did not interact with cytochrome P450 family members, thereby reducing potential important drug interactions.^{27,28} All patients received standard treatment every 3 weeks for up to six cycles: etoposide (120 mg/m² intravenously on day 1, then either the same on days 2 and 3 or 100 mg twice per day orally on days 2 and 3), with either cisplatin (60 mg/m² intravenously on day 1) or carboplatin (on day 1: area under curve [AUC] 5 or 6 using EDTA, or the Cockcroft and Gault method, to assess glomerular filtration rate). Radiotherapy was administered per local practice. Patients with limited disease were recommended to have concurrent chemoradiotherapy, preferably with the second chemotherapy cycle, or sequential chemoradiotherapy to the chest (the protocol did not specify dose), with prophylactic cranial radiation offered to those who achieved a partial response or complete tumor response (CR). Patients with extensive disease and who achieved CR were offered thoracic radiotherapy—recommended 40 Gy in 15 fractions over 3 weeks to the mediastinum and 25 Gy in 10 fractions over 2 weeks to the brain. All researchers and patients were blinded to statin and placebo. Primary care physicians of randomly assigned patients were contacted and asked not to prescribe statins while their patient was enrolled in the trial—so we did not collect data on statin use outside of the study.

Assessments

Clinical examinations, biochemical tests, and chest x-rays were performed at baseline, before each chemotherapy cycle, then every 2 months for the next year and every 3 months thereafter. Chest and abdomen computed tomography scans were performed at baseline, at the end of cycle 3, within 4 weeks of completing chemotherapy, and when clinically indicated thereafter. Brain scans were performed before random assignment, where indicated, to exclude patients with brain metastases who required immediate radiotherapy.

Statistical Analysis

The primary end point was OS, measured from the date of random assignment until death from any cause. Surviving patients were censored on the date last known to be alive. Secondary end points were progression-free survival (PFS), tumor response assessed by the treating clinician (Response Evaluation Criteria in Solid Tumors [RECIST] v1.0) and toxicity (Common Terminology Criteria for Adverse Events v3.0). PFS was calculated from the date of random assignment to the date of first progression or

death, whichever occurred first. OS and PFS were compared by using Cox proportional hazards regression models, adjusted for the randomization stratification factors, which were also preplanned subgroup analyses. Tablet adherence was assessed by a Wilcoxon test. The worst grade of adverse event for each patient and each toxicity type was used. All analyses were by intention-to-treat, except for adverse events, which were reported only for patients who took at least one dose of statin or placebo.

The trial was designed to detect an improvement in median OS with hazard ratio (HR) of 0.82 from an expected median in controls of 12 months, which corresponds to a difference in 2-year OS rates of 10% versus 15%. This required 842 patients (792 deaths) with 80% power and 5% two-sided significance.

RESULTS

Eight hundred forty-six patients were recruited between February 19, 2007 and January 3, 2012 (Fig 1). Of 1,537 patients who were screened, where screening logs were available, 338 (22%) patients were ineligible because they were recent or current statin users. Three randomly assigned patients who were later found to be ineligible were included in the analyses (intention-to-treat), because they had already started trial drug, which stopped within 6 months. Baseline characteristics were well balanced (Table 1). Median follow-up was 39.6 months.

Adherence

The median length of time on study drug was 8.6 months (pravastatin) and 7.8 months (placebo). Among 725 patients who started treatment and with available data on number of tablets dispensed and returned, the median number of tablets reportedly taken was 210 (pravastatin) and 181 (placebo; $P = .38$). Similarly, there was little difference found in the number of tablets returned (median, 38 and 36, respectively).

The amount of chemotherapy administered was similar between the two groups ($P = .19$); in each treatment arm, 57% received six cycles (Appendix Table A2, online only). There was little difference in the reasons for stopping chemotherapy early (Appendix Table A3, online only). The mean number of chemotherapy cycles was similar between patients with extensive disease (4.8) and limited disease (4.9).

Appendix Table A4 (online only) summarizes the types of additional treatments administered to patients after they finished chemotherapy, which were well balanced between the statin and placebo arms, and within patients with extensive and limited disease.

Efficacy

There were 758 deaths. Six hundred ninety-seven (92%) were a result of SCLC, including six deaths that were considered to be related to chemotherapy in the pravastatin group and none in the placebo group; eight deaths were attributed to a combination of cancer and treatment in the pravastatin arm and six in the placebo arm.

OS was similar between treatment groups (Fig 2), with medians of 10.7 months and 10.6 months for pravastatin and placebo, respectively, (unadjusted HR, 1.01 [95% CI, 0.88 to 1.16; $P = .90$] and adjusted for the stratification factors [1.02; 95% CI, 0.89 to 1.18; $P = .76$]). The corresponding 2-year OS rates were 14.1% (95% CI, 10.9 to 17.7) and 13.2% (95% CI, 10.0 to 16.7), respectively.

There were 787 PFS events. Median PFS was 7.7 months (pravastatin) versus 7.3 months (placebo), with unadjusted HR of 0.98 (95% CI, 0.85 to 1.13; $P = .81$), and adjusted HR of 1.01 (95% CI, 0.88 to 1.17; $P = .86$). The corresponding 1-year PFS rates were 25.3% and 24.2%, respectively; the 2-year PFS rates were 7.5% (95% CI, 5.2 to 10.3) and 7.2% (95% CI, 4.9 to 10.0), respectively.

Pravastatin also had no effect as a function of disease extent (Fig 3). Median OS was 14.6 months (pravastatin) versus

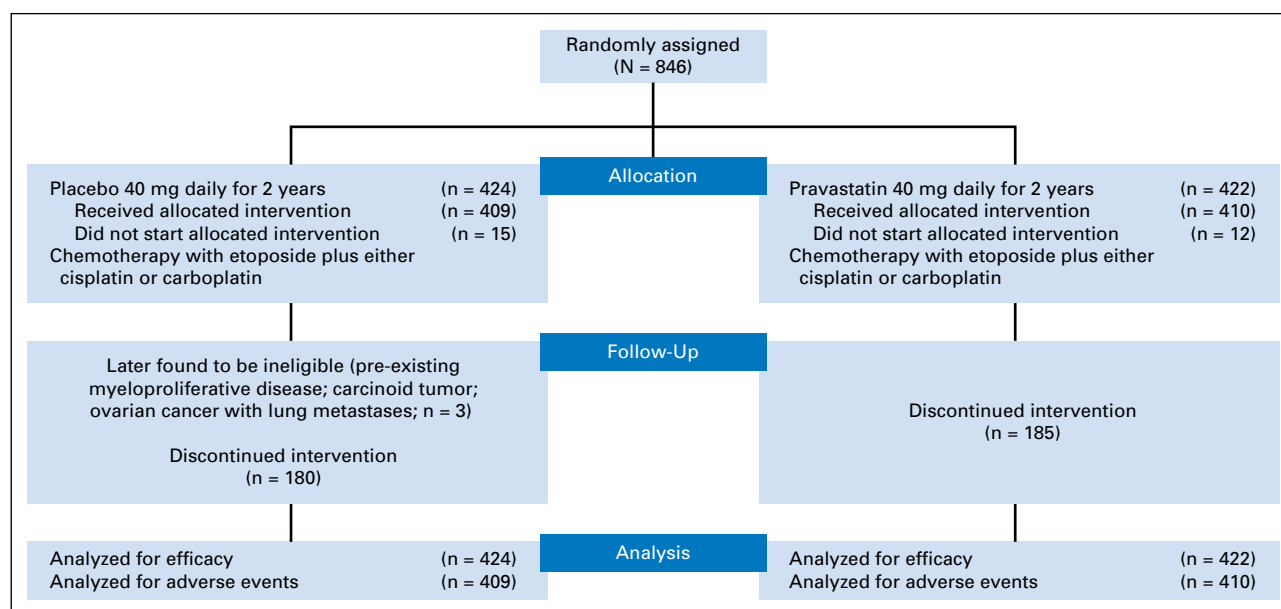


Fig 1. CONSORT diagram. Discontinued intervention includes patients who stopped statin and/or placebo early as a result of disease progression, toxicity, or patient and/or clinical decision.

Table 1. Baseline Patient Characteristics

Characteristic	Pravastatin (n = 422)	Placebo (n = 424)
Age at entry, median (range), years	64 (41-86)	63 (42-85)
Sex		
Male	219 (51.9)	214 (50.5)
Female	203 (48.1)	210 (49.5)
ECOG performance status		
0 or 1	319 (75.6)	319 (75.2)
2 or 3	103 (24.4)	105 (24.8)
Disease extent		
Limited disease	183 (43.4)	181 (42.7)
Extensive disease	239 (56.6)	243 (57.3)
Ipsilateral supraclavicular fossae (lymph nodes present)		
Absent	322 (76.3)	311 (73.3)
Present	97 (23.0)	105 (24.8)
No data	3 (0.7)	8 (1.9)
Ipsilateral pleural effusion		
No	317 (75.1)	310 (73.1)
Yes	104 (24.6)	108 (25.5)
No data	1 (0.2)	6 (1.4)
Chemotherapy regimen		
Carboplatin/etoposide	365 (86.5)	385 (90.8)
Cisplatin/etoposide	57 (13.5)	39 (9.2)
Metastatic site		
Same lung	3 (0.7)	9 (2.1)
Other lung	22 (5.2)	33 (7.8)
Liver	126 (29.9)	120 (28.3)
Adrenal glands	51 (12.1)	57 (13.4)
Lymph nodes	35 (8.3)	50 (11.8)
Skin	3 (0.7)	2 (0.5)
Other	65 (15.4)	62 (14.6)

NOTE. Data are given as No. (%) unless otherwise indicated. Smoking status was not collected as most patients were smokers.

14.6 months (placebo) for limited stage disease, and 9.1 months versus 8.8 months for extensive stage (interaction $P = .53$). Furthermore, no subgroup effects were observed for performance status, age, sex, type of platinum therapy administered, pleural effusion, or presence of affected lymph nodes (Appendix Fig A1, online only). Allowing for a slight imbalance between the two arms for type of platinum treatment (Table 1)

made little difference to the results (HR, 1.04; 95% CI, 0.90 to 1.19; $P = .63$).

Tumor response was similar between trial groups with 29 (69.0%) of 422 patients on pravastatin and 293 (69.1%) of 424 patients on placebo achieving a partial or complete (best) overall response; there was little difference in response rates for limited and extensive stage disease (Appendix Table A5, online only).

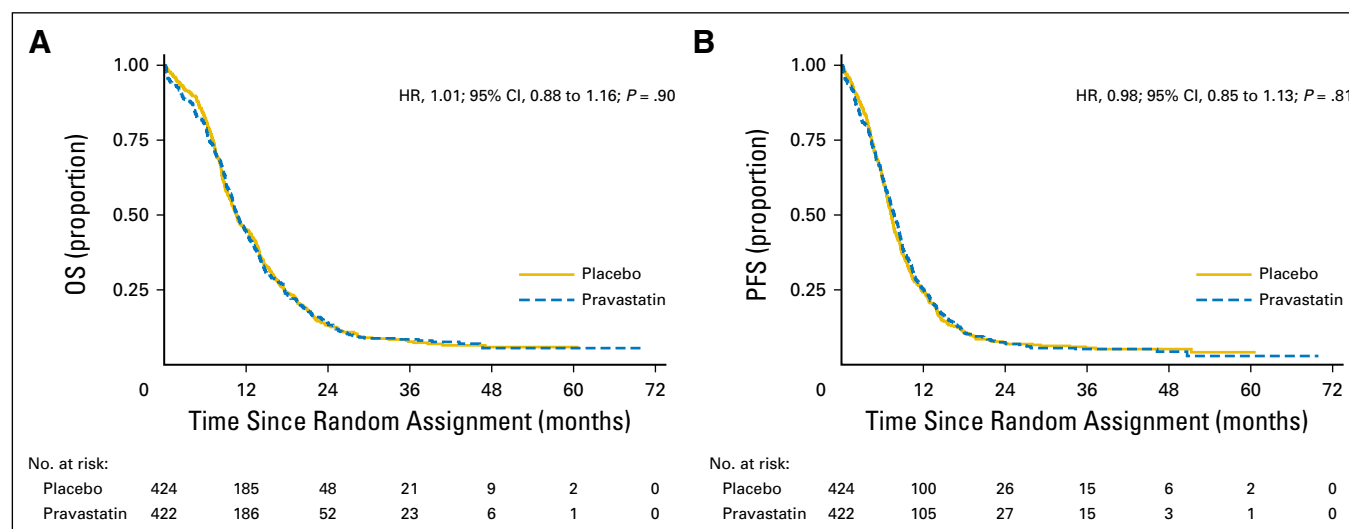


Fig 2. (A) Overall survival (OS) and (b) progression-free survival (PFS). The number of events in the pravastatin versus placebo groups were 381 versus 377 deaths, and 395 versus 392 PFS events, respectively. HR, hazard ratio.

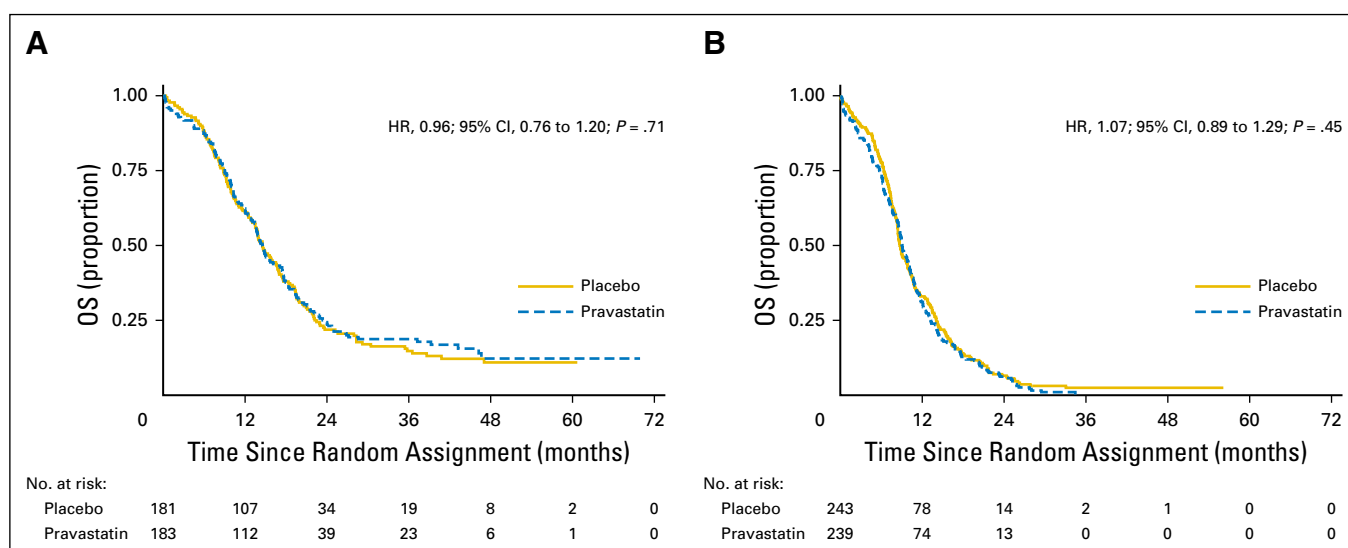


Fig 3. Overall survival (OS) in patients with (A) limited stage and (B) extensive stage disease. HR, hazard ratio.

The number of patients who received thoracic radiotherapy was similar between trial groups with 202 (47.9%) patients in the pravastatin arm and 210 (49.5%) in the placebo arm, with a corresponding median total dose of 39 Gy (range, 3 to 66) and 40 Gy (range, 2 to 66), respectively. Furthermore, 203 (48.1%) patients in the pravastatin arm and 207 (48.8%) patients in the placebo arm received prophylactic cranial brain irradiation, with corresponding median total dose of 25 Gy (range, 2 to 40) and 25 Gy (range, 2 to 56), respectively.

Adverse Events

Table 2 shows that the distribution of grade 3 to 5 adverse events was similar between the pravastatin and placebo arms with

333 (81.2%) of 410 patients versus 333 (81.4%) of 409 patients, respectively ($P = .94$). The most common grade 3 to 5 adverse event was neutropenia, which affected 184 (44.9%) of patients in the pravastatin arm and 176 (43.0%) of patients in the placebo arm. Myalgia or myositis of any grade—recognized toxicities of statins—occurred in 74 patients in the pravastatin arm and 77 patients in the placebo arm; the majority of these were grade 1 or 2, with three patients who received pravastatin experiencing grade 3 and 4 (three grade 3, one grade 4) compared with three patients who received placebo (all grade 3). GI bleeding (grade 1) was experienced by three patients in the statin group, in addition to two (grade 2) and one (grade 3) events. GI bleeding (grade 1) was experienced by two patients in the placebo group in addition to two (grade 2) events.

Table 2. Worst Grade of Adverse Events for Each Patient (grade ≥ 3)

Variable	Pravastatin (n = 410)	Placebo (n = 409)	P
Any grade 3 to 5	333 (81.2)	333 (81.4)	.94
Grade 3	166 (40.5)	170 (41.6)	.75
Grade 4	148 (36.1)	148 (36.2)	.98
Grade 5	19 (4.6)	15 (3.7)	.49
Common adverse events			
Neutropenia	184 (44.9)	176 (43.0)	
Leucopenia	62 (15.1)	52 (12.7)	
Fatigue	61 (14.9)	53 (13.0)	
Pain	52 (12.7)	49 (12.0)	
Infection (clinically documented)	51 (12.4)	49 (12.0)	
Dyspnea	50 (12.2)	45 (11.0)	
Anemia	46 (11.2)	44 (10.8)	
Thrombocytopenia	47 (11.5)	39 (9.5)	
Infection, other	40 (9.8)	44 (10.8)	
Neutrophils	39 (9.5)	35 (8.6)	
Thrombosis/thrombus/embolism	23 (5.6)	28 (6.8)	
Hyponatremia	23 (5.6)	22 (5.4)	
Haemoglobin	21 (5.1)	22 (5.4)	
Febrile neutropenia	22 (5.4)	18 (4.4)	
Myalgia/myositis	3 (0.7)	4 (1.0)	
Pneumonitis	1 (0.2)	2 (0.5)	
Oesophagitis	3 (0.7)	4 (1.0)	

NOTE. Data are given as No. (%) unless otherwise indicated.

DISCUSSION

To our knowledge, LUNGSTAR, by far, is the largest randomized trial of statin therapy in patients with cancer reported to date. Use of placebo avoids an important bias present in observational studies. Although pravastatin was safe, with high adherence—patients tended to continue until disease progression—it did not improve outcomes in patients with SCLC, nor in those with limited stage or extensive stage disease.

When LUNGSTAR was developed in 2005, preclinical evidence was sufficient, though not considered overwhelming by some; however, rather than perform further experimental and/or preclinical studies, followed by phase II, then phase III trials, the investigators and funder (Cancer Research UK) decided to launch a definitive large study sooner rather than later, given the growing evidence in this field at the time. The independent data monitoring committee reviewed efficacy during the trial. In April 2010, when 25% of the target number of deaths was observed, conditional power (CP) for OS was 66%—CP is the chance of obtaining the target HR of 0.82 if the trial continued to the end, given the data thus far. In February 2011, with 655 patients recruited and 41% of events, CP was 11% for OS, but 30% for PFS, which was not considered low enough to stop the study early, even though it was a secondary end point. Additional important reasons for finishing accrual were to have a large study size with convincing results, whether positive or negative, particularly given the accumulating positive observational studies, and to ensure sufficient patient numbers for limited disease and extensive disease in case pravastatin was effective for one and not the other.

Various possibilities might explain our findings, including dose, type of statin, or that our mechanistic understanding was too simplistic. When our study was established, the maximum pravastatin dose was 40 mg, which seemed to be effective in a randomized cancer trial¹²; however, this dose might be too low and the current 80 mg maximal dose could have achieved efficacy. Alternatively, hydrophilic statins, such as pravastatin, may not be as effective as lipophilic agents, such as simvastatin; some studies have suggested clearer benefits for simvastatin in lung cancer,²¹ with a lack of benefit for pravastatin in cancer prevention or cancer death observed in a trial of patients with coronary heart disease.²⁹ However, there is insufficient evidence to reliably conclude whether any one type of statin is better than another, and biologic plausibility for a difference is lacking.²² Of interest, more recent evidence in glioma cells has suggested that statins may fail to work in certain cancer cells because of a phosphatidylinositol 3-kinase-mediated pathway connected to LDL receptors.^{30,31} It is unclear whether this might impact the responsiveness to statins of other cancers. Another study limitation is that blood lipid levels were not measured as part of routine biochemistry for managing patients with SCLC, which would have unblinded the trial, and we did not secure funds to measure cholesterol and other relevant markers from stored samples; therefore, we are unable to correlate these or other factors, such as HMG-CoA reductase levels, in tumor biopsies with outcomes at present.

We compared patient outcomes in LUNGSTAR with others. Our observed median OS (10.7 months) is similar to that observed in another United Kingdom trial of SCLC (comparing thalidomide

with placebo, but little difference was found), which had a similar mix (approximately one half) of limited stage and extensive stage disease (median 10.5 months).³² However, survival for limited stage patients (median 14.6 months LUNGSTAR, 12.1 months in the thalidomide trial), is less than observed in a recent radiotherapy trial (median OS, 25 to 30 months),³³ probably because it enrolled patients from several countries, where more radiotherapy has been given than in the United Kingdom in previous years.

We conducted a systematic literature review to identify all randomized trials that were specifically designed to evaluate lipid-lowering therapies among patients with cancer using MEDLINE (1966 to March 2016), and the keywords 'lipid', 'cholesterol', 'statin' (and specific names), and 'tumor/tumor', 'cancer', 'carcinoma', 'adenocarcinoma' and 'random.' There were only 10 trials^{12,34-42} (9 of statins), which are summarized in Table 3. LUNGSTAR is three times larger than any other randomized trial, the next largest having enrolled 283 patients. The 9-month OS improvement for pravastatin in the earlier trial by Kawata et al¹² was probably the result of a lack of blinding and small study size ($n = 83$). Of importance, there are now five published double-blind studies of statins in patients with cancer, including ours (SCLC, gastric, pancreas, colorectal, and precancerous melanoma lesions), of which one used pravastatin, one lovastatin, and three simvastatin, and none showing statins of various types to be effective.³⁶⁻³⁹

We also found a single-arm, phase II trial and a non-randomized, unblinded trial in patients with lung cancer. One was for previously untreated extensive-disease SCLC ($n = 61$) in which simvastatin plus irinotecan and etoposide produced a 1-year OS rate of 39.3% (target 45%); median OS and PFS were 11.0 months and 6.1 months, respectively, which was similar to current treatments.⁴³ The other trial included patients with stage III and IV cancer without SCLC, whose tumors were KRAS-mutant and epidermal growth factor receptor wild-type, reported better outcomes for 12 patients treated with a tyrosine kinase inhibitor plus either simvastatin or atorvastatin compared with 55 who received tyrosine kinase inhibitor alone. In that study the PFS was 2.0 months versus 1.0 month ($P = .025$), and OS 14.0 months versus 5.4 months ($P = .13$); however, it was not reported why those patients received a statin, hence there could be important confounders not allowed for.⁴⁴

Most prior studies that have reported benefits for statins were observational, with inherent design problems, including confounding and bias.⁴⁵ Time-related biases are particularly concerning.⁴⁶ Immortal time bias occurs when there is a length of time between the start of follow-up and a subsequent start of statin therapy, which is counted in the total follow-up time for a participant—but during which the participant is actually unexposed—and, thus, it seems that this participant has survived longer than a control (non-statin user). Jeon et al⁴⁷ show how this bias can spuriously create an association by using studies of patients with liver cancer in which the OS HR for statin use versus nonuse was 0.84 ($P = .047$) before and 0.98 ($P = .82$) after allowance for this bias. Randomized controlled trials, such as LUNGSTAR, avoid these issues.

Preclinical studies continue to report positive effects for statins in lung cancer cell lines with regard to reduced proliferation,^{48,49} reduced migration,⁵⁰ increased apoptosis,⁴⁹ and reduced tumor

Table 3. Prospective Randomized Clinical Trials of Anticancer Therapy With or Without Statin or Lipid-Lowering Therapy Among Patients With Cancer¹

Study	Trial Phase	Cancer Diagnosis	Previously Treated	Statin/Other	Placebo	Standard Therapy	No. of Patients	Median Overall Survival, Months			Median Progression-Free Survival, Months		
								Statin	Control	HR, <i>P</i>	Statin	Control	HR, <i>P</i>
Trials showing a benefit for statins													
Thomas et al ³⁴	II	Prostate	Yes	Polyphenol-rich*	Yes	None given†	283	Median increase in PSA was 14.7% (active) and 78.5% (placebo) at 6 months; <i>P</i> < .001					
Kawata et al ¹²	II	Advanced liver	No	Pravastatin 40 mg	No	TAE, FU	83	18	9	0.50, <i>P</i> = .006	Ki-67 (marker of tumor proliferation) reduced CC3 (marker of apoptotic activity) increased Both statistically significant No difference between 20 mg and 80 mg groups		
Garwood et al ³⁵	II	DCIS or stage I breast	No	Fluvastatin 20 mg v 80 mg	No	Statin given for 3-6 weeks before surgery	40						
Trials showing no benefit for statins													
Kim et al ³⁶	III	Advanced gastric	No	Simvastatin 40 mg	Yes	Capecitabine, cisplatin	244	11.6	11.5	0.97, <i>P</i> = .82	5.2	4.6	0.93, <i>P</i> = .66
Hong et al ³⁷	II	Advanced pancreas	No	Simvastatin 40 mg	Yes	Gemcitabine	114	6.6	8.9	<i>P</i> = .74	2.4	3.6	1.5, <i>P</i> = .90
Linden et al ³⁸	II	Premelanoma (atypical nevi)	Yes	Lovastatin 40 mg then 80 mg	Yes	None given	80	Primary end point was regression of atypical nevi: mean increase of 0.50 (statin) v mean decrease of 0.12 (placebo); <i>P</i> = .048					
Lim et al ³⁹	III	Metastatic colorectal	Yes	Simvastatin 40 mg	Yes	XELIRI/FOLFIRI	269	15.3	19.2	<i>P</i> = .83	5.9	7.0	1.03, <i>P</i> = .86
Konings et al ⁴⁰	II	Unresectable gastric	No	Pravastatin 40 mg	No	Epirubicin, cisplatin, capecitabine	30	8	6	<i>P</i> > .05	6	5	<i>P</i> > .05
Han et al ⁴¹	II	Advanced NSCLC	Yes	Simvastatin 40 mg	No	Gefitinib	106	13.6	12.0	0.88, <i>P</i> = 0.49	33.3% Target	46.7% Target	0.89, 0.55
Limburg et al ⁴²	II	Prior resected colon	Yes	Atorvastatin 20 mg	No	None given	44	39.3% Target	45% Target	Primary endpoint was number of aberrant crypt foci: no difference between statin and controls (<i>P</i> = .92) No difference in change in Ki-67			

NOTE: Studies are ordered by conclusion and the use of placebo or not. One trial was precancer.
Abbreviations: DCIS, ductal carcinoma in situ; FOLFIRI, folinic acid, fluorouracil, and irinotecan; FU, fluorouracil; HR, hazard ratio; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; PSA, prostate specific antigen; TAE, transarterial embolization; TTP, time to progression; XELIRI, Capecitabine and Irinotecan.
*Tablet containing pomegranate, green tea, broccoli, and turmeric. Although this trial was not directly relevant to statins (it was meant to be a form of lipid reduction) we wanted to be inclusive.
†Active surveillance or watch and wait.

growth.⁵⁰ There are also several ongoing trials of statins in various cancers (eg, ClinicalTrials.gov: NCT02360618, NCT01980823, NCT01038154, NCT02161822, NCT02483871, NCT02569645, and NCT02029573). Given the findings from our trial and the other published, double-blind, randomized controlled trials, independent data monitoring committees of studies that are still recruiting or in follow-up should examine interim analyses of clinical end points and stop early if there is sufficient evidence for futility, thus saving resources. Trials of statins in patients with cancer, which require an unexposed control group, will become more difficult to conduct because the usual age group of patients with cancer (middle and old age) already take them, as seen in LUNGSTAR, in which 22% of screened patients were ineligible because they were recent or current statin users.

In summary, we found no value for pravastatin when combined with standard platinum chemotherapy in patients with SCLC. Ongoing and future trials of statins used for either cancer prevention or treatment should monitor clinical efficacy, and for planned studies of patients with cancer, investigators should ensure preclinical evidence is sufficient enough to warrant large-scale randomized studies.

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Appendix

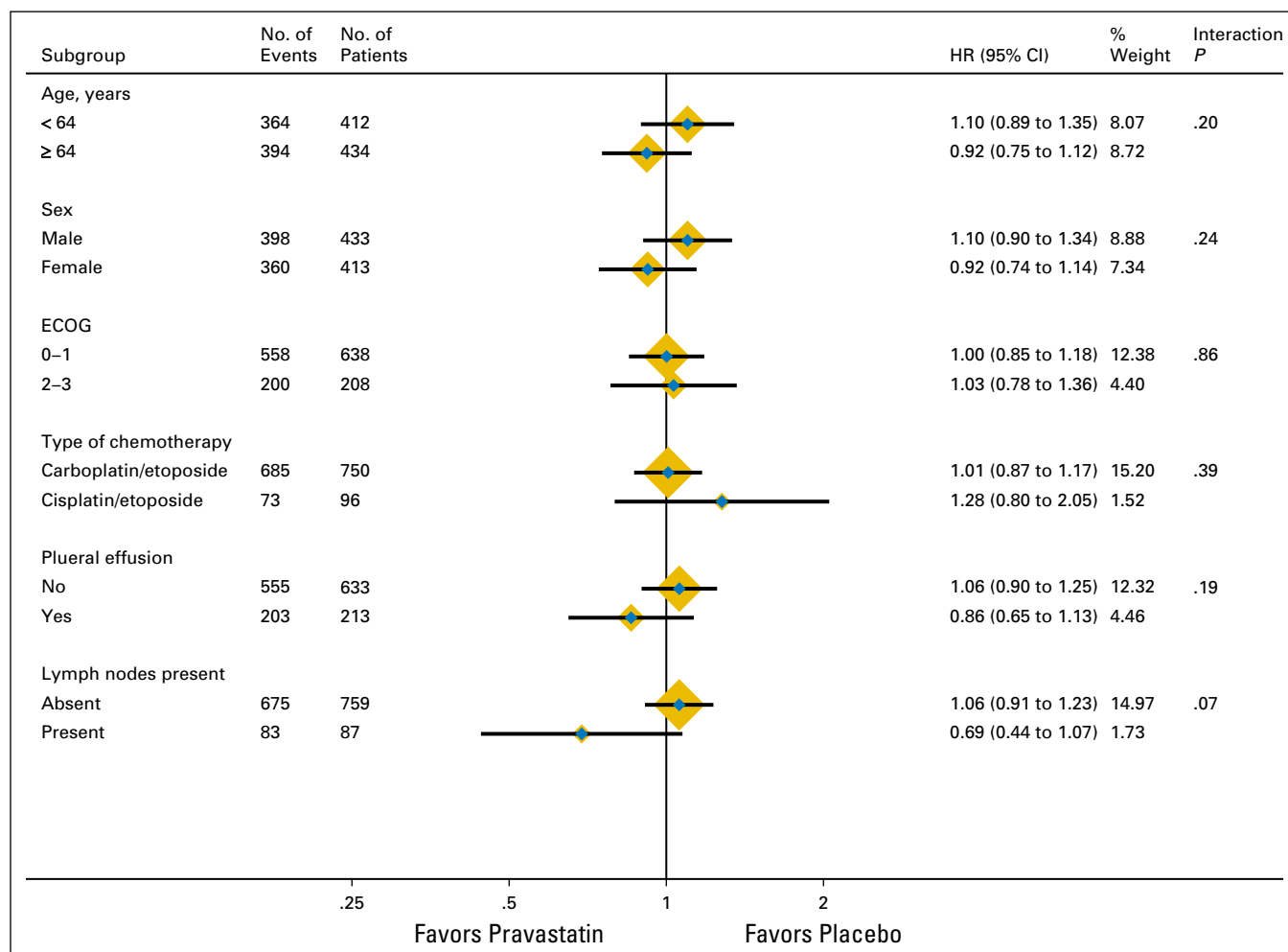


Fig A1. Forest plot showing subgroup analyses (overall survival). ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.

Table A1. Recruiting Centers and Principal Investigators

Hospital	Investigator	Hospital	Investigator
Aberdeen Royal Infirmary	Marianne Nicolson	Queen Elizabeth Hospital (King's Lynn)	Kathryn Waite
Addenbrooke's Hospital	Susan Harden	Queen Elizabeth Hospital (Woolwich)	Shahreen Ahmad
Airedale General Hospital	Michael Crawford	Queen Elizabeth the Queen Mother Hospital	Russell Burcombe
Birmingham Heartlands Hospital	Joyce Thompson	Queen's Hospital (Burton-on-Trent)	A.D. Chetiyawardana
Bradford Royal Infirmary	Andy Conn	Royal Berkshire Hospital	Helen O'Donnell
Bronglais General Hospital	Sajid Durrani	Royal Bournemouth Hospital	Thomas Geldart
Broomfield Hospital	Neville Davidson	Royal Derby Hospital	P. Pattu
Castle Hill Hospital	Michael Lind	Royal Devon and Exeter Hospital	Elizabeth Toy
Charing Cross Hospital	Michael Seckl	Royal Gwent Hospital	Alison Brewster
Cheltenham General Hospital	David Farrugia	Royal Hampshire County Hospital	Clare Green
City Hospital, Birmingham	David Peake	Royal Shrewsbury Hospital	Anirban Chatterjee
Clatterbridge Centre for Oncology	Ernest Marshall	Royal Sussex County Hospital	Joanna Simpson
Darent Valley Hospital	Riyaz Shah	Royal United Hospital	Olivia Frim
Derbyshire Royal Infirmary	Rajeev Kaushal	Salisbury District Hospital	Adityanarayan Bhatnagar
Derriford Hospital	Amy Roy	Sandwell General Hospital	David Peake
Diana Princess of Wales Hospital	Sunil Upadhyay	Scarborough Hospital	Amandeep Dhadha
Dorset Cancer Centre, Poole	Mike Bayne	Scunthorpe General Hospital	Sunil Upadhyay
Dorset County Hospital	Mike Bayne	Singleton Hospital	Kath Rowley
Essex County Hospital	Dakshinamoorthy Muthukumar	South Tyneside District General Hospital	Liz Fuller
Falkirk and District Royal Infirmary	Nicola Steele	Southampton General Hospital	Christian Ottensmeier
Freeman Hospital, Newcastle	Jill Gardiner	St George's Hospital, London	Tim Benepal
Glan Clwyd Hospital	Angel Garcia	St James's University Hospital	Michael Snee
Good Hope Hospital	Shobhit Baijal	St Luke's Cancer Centre	Marianne Illsley
Guy's Hospital	Ana Montes	St Mary's Hospital, Isle of Wight	Umapathy Hombaiah
Harrogate and District Hospital	Samuel Chan	St Richard's Hospital	Suhail Baluch
Hereford County Hospital	Nick Reed	Stoke Mandeville Hospital	Nicholas Bates
Huddersfield Royal Infirmary	Barbara Crosse	The Christie Hospital	Fiona Blackhall
Ipswich Hospital	Jarney Morgan	Torbay Hospital	Nicole Dorey
James Cook University Hospital	Clive Peedell	University College London Hospital	Siow Ming Lee
Kent and Canterbury Hospital	Russell Burcombe	University Hospital Aintree	Julie O'Hagan
King's Mill Hospital	Ivo Hennig	University Hospital Birmingham	Qamar Ghafoor
Leicester Royal Infirmary	Samreen Ahmed	University Hospital of North Durham	Rhona McMenemin
Lister Hospital	Andreas Polychronis	Velindre Hospital	Jason Lester
Llandough Hospital	Jason Lester	West Wales General Hospital	Margaret Wilkins
Luton and Dunstable Hospital	Peter Hoskin	Weston General Hospital	Serena Hilman
Maidstone Hospital	Riyaz Shah	Wexham Park Hospital	James Gildersleve
Manor Hospital, Walsall	A.D. Chetiyawardana	Whiston Hospital	Ernest Marshall
Milton Keynes General Hospital	Hany Eldeeb	Whittington Hospital	Pauline Leonard
Mount Vernon Hospital	Jeanette Dickson	William Harvey Hospital	Russell Burcombe
North Devon District Hospital	Mark Napier	Withybush General Hospital	Vallipuram Vigneswaran
Northampton General Hospital	Hany Eldeeb	Worcestershire Royal Hospital	David Farrugia
Nottingham City Hospital	Vanessa Potter	Worthing Hospital	Sankha Mitra
Peterborough District Hospital	Kate Fife	Wycombe Hospital	Nicholas Bates
Princess Royal University Hospital	Ana Montes	Wythenshawe Hospital	Paul Taylor
Queen Alexandra Hospital	Sethupathi R. Muthuramalingam	Yeovil District Hospital	Maria Karina
		York District Hospital	Sam Chan

Table A2. Compliance to Chemotherapy

	Pravastatin (n = 422)	Placebo (n = 424)
None	4 (0.9)	6 (1.4)
At least 1 cycle	418 (99.1)	418 (98.6)
At least 2 cycles	385 (91.2)	398 (93.9)
At least 3 cycles	370 (87.7)	373 (88.0)
At least 4 cycles	341 (80.8)	351 (82.8)
At least 5 cycles	270 (64.0)	281 (66.3)
6 cycles	241 (57.1)	241 (56.8)

NOTE. Data are given as No. (%). $P = .19$ for differences between the two groups.

Pravastatin and Chemotherapy in Small-Cell Lung Cancer

Table A3. Reasons for Stopping Chemotherapy Before Four Cycles

	Pravastatin (n = 71)	Placebo (n = 70)
Comorbid condition	5	6
Haematological condition	9	5
Clinician decision	28	24
Patient decision	1	2
Progressive disease	4	3
Other toxicity	11	14
Other/unknown	13	16

NOTE. Data are given as No.

Table A4. Additional Treatments Given to Patients After Finishing Initial Chemotherapy or After Progression

	Pravastatin	Placebo
Limited disease	183	181
Thoracic radiotherapy	117 (64)	127 (70)
Radiotherapy elsewhere	39 (21)	41 (23)
Prophylactic cranial irradiation	100 (55)	107 (59)
Chemotherapy	52 (28)	52 (29)
Biologic agents	0	0
Extensive disease	239	243
Thoracic radiotherapy	86 (36)	83 (34)
Radiotherapy elsewhere	62 (26)	54 (22)
Prophylactic cranial irradiation	103 (43)	100 (41)
Chemotherapy	70 (29)	67 (28)
Biologic agents	1 (0.4)	0

NOTE. Data are given as No. (%).

Table A5. Best Overall Tumor Response (all patients)

	Pravastatin (n = 422)	Placebo (n = 424)
All patients		
Complete response	25 (5.9)	20 (4.7)
Partial response	266 (63.0)	273 (64.4)
Stable disease	37 (8.8)	55 (13.0)
Progressive disease	28 (6.6)	22 (5.2)
Not evaluable	66 (15.6)	54 (12.7)
Patients with limited disease		
Complete response	19 (10.4)	11 (6.1)
Partial response	113 (61.7)	111 (61.3)
Stable disease	21 (11.5)	28 (15.5)
Progressive disease	6 (3.3)	6 (3.3)
No data	24 (13.1)	25 (13.8)
Patients with extensive disease		
Complete response	6 (2.5)	9 (3.7)
Partial response	153 (64.0)	162 (66.7)
Stable disease	16 (6.7)	27 (11.1)
Progressive disease	22 (9.2)	16 (6.6)
No data	42 (17.6)	29 (11.9)

NOTE. Data are given as No. (%).